REMARKS

I. Amendments to the Claims:

Claims 29-33, 36-42, 45, 47-50, 80-82, 92-100 and 103 are pending and under examination in this application. Claims 34, 43, 46, 51, 53-59, 61-68, 70-78, 84-86, 91, and 101 were withdrawn as being drawn to a non-elected invention.

Claim 31 has been canceled without prejudice. Claims 29, 93-94, 99, 100, and 103 are currently amended herein. Support for the claim amendments can be found throughout the application as filed. Accordingly, no new matter has been added.

Upon entry of the instant amendments to the claims, claims 29-30, 32-33, 36-42, 45, 47-50, 80-82, 92-100 and 103 will be pending and under examination in the instant application.

II. Claim Objections:

Claims 93-94 were objected to for reciting embodiments of a non-elected invention.

Claims 93 and 94 have been amended to delete reference to claims 63 and 55, respectively. Accordingly, this objection has been rendered moot.

III. Rejection Under 35 U.S.C. § 102(b):

Claims 29-30, 32-33, 36-37, 39-40, 92, 95, 99-100 and 103 were rejected under 35 U.S.C. § 102(e) as purportedly being anticipated by Slavin (U.S. 6,544,787) as evidenced by Fredrickson *et al.* (*Developmental and Comparative Immunology*, **18**:251-263 (1994)). (*see,* Office Action, page 3).

For a reference to anticipate a claimed invention in terms of 35 U.S.C. § 102, the prior art must teach ***each and every element*** of the claimed invention. *Lewmar Marine v. Barient*, 827 F.2d 744, 3 USPQ2d 1766 (Fed. Cir. 1987).

Independent claims 29, 99, 100, and 103, as amended, recite, in relevant part, "reactivating the thymus of the patient, the thymus being reactivated by disruption of sex steroid-mediated signaling to the thymus." These independent claims have been amended to include the limitation (underlined portion) recited in claim 31, which was not rejected in the Office Action of January 17, 2008.

Accordingly, in view of the instant amendments to the claims, Applicant respectfully requests that the Examiner reconsider and withdraw this rejection under 35 U.S.C. § 102(e). Likewise, the rejection of dependent claims 30-33, 36-42, 45, 47-50, 80-82, 92-98, and 101 which contain all the limitations of independent claims 29, 99, 100, and 103, as amended, should be reconsidered and withdrawn.

IV. Rejections Under 35 U.S.C. § 103(a):

(a) Claims 29-33, 36-42, 45, 47-50, 92-100 and 103 were rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Sykes *et al.* (U.S. 5,658,564) in view of Slavin (U.S. 6,544,787), Nowak (New Scientist 19/26, page 11, January 2, 1999), and Mathias (U.S. 5,434,136). (*see,* Office Action, page 5).

To establish a *prima facie* case of obviousness under 35 U.S.C. § 103(a), the Examiner must: (i) show that the combination of references discloses all the elements of the claim; (ii) advance "a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the new invention does . . . " *KSR International Co. v. Teleflex, Inc.*, 127 S. Ct. 1727, 1731 (2007); and (iii) show a reasonable likelihood of success.

Applicant respectfully submits that the combined references do not render Applicant's claimed invention for the reasons detailed below.

There are four pending independent claims under examination, all of which have been amended in this Amendment.

Amended independent claim 29 is directed to a method for treating or alleviating symptoms of an autoimmune disease in a patient having or suffering an autoimmune disease, comprising: depleting T cells in the patient; and reactivating the thymus of the patient, the thymus being reactivated by disruption of sex steroid-mediated signaling to the thymus, wherein the patient has an improved prognosis for the autoimmune disease compared to an untreated patient suffering from the autoimmune disease.

Amended independent claim 99 is directed to a method for treating or alleviating symptoms of an autoimmune disease in a patient having or suffering an autoimmune disease,

comprising reactivating the thymus of the patient, the thymus being reactivated by disruption of sex steroid-mediated signaling to the thymus, wherein the patient has an improved prognosis for the autoimmune disease compared to an untreated patient suffering from the autoimmune disease.

Amended independent claim 100 is directed to a method for treating or alleviating symptoms of an autoimmune disease in a patient having or suffering an autoimmune disease, comprising: providing the patient with immunosuppressive therapy; and reactivating the thymus of the patient, the thymus being reactivated by disruption of sex steroid-mediated signaling to the thymus, wherein the patient has an improved prognosis for the autoimmune disease compared to an untreated patient suffering from the autoimmune disease.

Amended independent claim 103 is directed to a method for reducing the risk of developing an autoimmune disease in a patient at risk of having or suffering an autoimmune disease, comprising: depleting T cells in the patient; and reactivating the thymus of the patient, the thymus being reactivated by disruption of sex steroid-mediated signaling to the thymus, wherein the patient has a reduced risk of developing the autoimmune disease compared to an untreated patient at risk of having or suffering from the autoimmune disease.

Applicant respectfully submits that the Office Action has not set forth a *prima facie* case of obviousness because the Office Action: (i) fails to show that the combination of references discloses all the elements of Applicant's claims; (ii) fails to provide a motivation to modify the primary reference with the secondary references; and (iii) fails to show a reasonable likelihood of success.

The Office Action fails to show that the combination of references discloses all the elements of Applicant's claims because the combined references simply fail to teach the treatment of a patient with autoimmune disease by, in relevant part, reactivating the thymus ***of the patient***, wherein the thymus is reactivated by disruption of sex-steroid signaling to the thymus. There is simply no teaching or suggestion in the combined references of treating any autoimmune disease by Applicant's claimed method.

The Office Action also fails to provide sufficient motivation to modify the primary reference with the secondary references.

The primary reference relied upon by the Officer Action, Sykes, is directed to ***the replacement*** of thymus function and to the induction or restoration of immunological tolerance. (*see,* Abstract). Applicant's claimed invention relates to treating an autoimmune disease by depleting T cells in a patient and reactivating the thymus. The primary reference does not refer to two essential features of the claimed invention, namely, treating an autoimmune disease and reactivating the thymus of the patient (Sykes teaches providing thymic tissue from a source other than the patient). Specifically, Sykes teaches:

> It has been discovered that host T cells of an ***athymic*** T cell depleted host ***which has received a thymic graft***, e.g., a xenogeneic thymic gaff [*sic*], can mature ***in the donor thymic tissue***, e.g., in xenogeneic thymic tissue. Host T cells which mature in the implanted xenogeneic thymic tissue are immunoincompetent. (*see,* col. 1, ll. 31-37). (emphasis added).
>
> The invention includes the steps of introducing into the primate host, ***donor thymic tissue***, e.g., xenogeneic thymic tissue, preferably fetal or neonatal thymic tissue, so that host T cells can mature ***in the implanted thymic tissue.*** (*see,* col. 1, ll. 46-50). (emphasis added).
>
> . . . the recipient is ***thymectomized,*** preferably before or at the time the xenograft thymic tissue is introduced. (*see,* col. 1, ll. 65-67). (emphasis added).

In other words, Sykes is directed to restoration of immunological tolerance in a host without a thymus. Sykes' method involves providing the host with donor thymic tissue and permitting host T cells to mature in the donor thymic tissue. Applicant's invention, on the other hand, relates to reactivating the existing thymus ***of the patient***. Sykes' method in no way suggests reactivating the thymus ***of the patient***, or treating an autoimmune disease. To arrive at Applicant's claimed invention, the Office Action attempts to fill these two significant gaps between the cited art and claimed invention by citing documents that mention somewhere treating an autoimmune disease or reactivating the thymus of the patient. However, the Office Action was unable to cite a document that even taught these two features in a single source.

The secondary reference, Slavin, relates to methods of reducing patient anti-donor responsiveness in treating various diseases including autoimmune diseases. Slavin makes no

mention of the benefits of reactivating the patient's thymus of the patient to treat an autoimmune disease. Furthermore, there is no mention of reactivating the thymus of a patient with an autoimmune disease by disruption of sex steroid-mediated signaling to the thymus.

The secondary reference, Nowak, is secondhand information written by a journalist (not one with skill in the art) which provides no scientific data. Most importantly, Nowak does not mention treating autoimmune disease, let alone the additional step of depleting T cells in the patient or providing the patient with immunosuppressive therapy prior to reactivating the thymus.

Finally, the secondary reference, Mathias, relates to treating motility disorders. As outlined in column 2, lines 32-35 of this patent, motility disorders are "secondary disorders associated with autoimmune disorders" (emphasis added). Thus, Mathias does not teach or suggest treating an autoimmune disease *per se*, let alone depleting T cells in a patient and reactivating the thymus of a patient with an autoimmune disease by disruption of sex steroid-mediated signaling to the thymus.

In sum, the teachings of the cited references taken alone or in combination do not teach or suggest reactivating the existing thymus ***of the patient*** to treat an autoimmune disease.

Furthermore, MPEP § 2143.01 (VI) states that: "If the proposed modification or combination of the prior art would change the principle of operation of the prior art invention being modified, then the teachings of the references are not sufficient to render the claims *prima facie* obvious." *In re Ratti*, 270 F.2d 810, 123 USPQ 349 (CCPA 1959). Because the Sykes' patent's principle of operation is based on permitting host T cells to mature in ***donor*** thymic tissue, the Office Action's proposed modification (reactivating the thymus of the patient) would modify Sykes' principle of operation. Thus, according to MPEP § 2143.01 (VI), such a modification would not be *prima facie* obvious.

Although the combined teachings of all four references in no way suggest treating an autoimmune disease by depleting T cells (or providing the patient with immunosuppressive therapy) in a patient and reactivating the thymus of the patient, it is also important to note that combining the cited references to attempt to arrive at Applicant's claimed invention is based on

mere hindsight analysis. This is exemplified by the primary reference not mentioning two essential features of the claimed invention, namely treating an autoimmune disease and reactivating the thymus of the patient. It seems that all the Office Action has done is search for any documents that refer to one or both of these features without providing any scientific reason why the skilled person would have been motivated to modify, in a significant manner, the teachings of Sykes. Furthermore, no scientific reason has been provided why, without the benefit of hindsight, the skilled person would have even considered performing the claimed invention when considering the cited documents alone or in combination. "Combining prior art references without evidence of such a suggestion, teaching, or motivation simply takes the inventor's disclosure as a blueprint for piecing together the prior art to defeat patentability – the essence of hindsight." *In re Dembiczak*, 175 F.3d 994, 999, 50 USPQ2d 1614, 1617 (Fed. Cir. 1999). Applicants respectfully contend that the Applicant's disclosure has been improperly used as a blueprint for piecing together the prior art to attempt to defeat patentability of Applicant's claimed invention.

Finally, Applicant notes that even if the references were to be combined as set forth by the Office Action there is simply no expectation of success. There is simply no teaching in the combined references that reactivating the thymus of the patient would lead to treating a patient with an autoimmune disease.

For the foregoing reasons, Applicant respectfully submits that the grounds for this rejection have been overcome. Accordingly, Applicant respectfully requests that the Examiner reconsider and withdraw the rejection of independent claims 29, 99, 100, and 103. Likewise, the rejection of dependent claims 30-33, 36-42, 45, 47-50, 92-98, and 101, which contain all the limitations of independent claims 29, 99, 100, and 103, as amended, should be reconsidered and withdrawn.

(b) Claims 80-81 were rejected as purportedly being obvious over Sykes *et al.* (U.S. 5,658,564) in view of Slavin (U.S. 6,544,787), Nowak (New Scientist 19/26, page 11, January 2,

1999), and Mathias (U.S. 5,434,136), and further in view of Bolotin *et al.* (Blood **88**:1887-1894 (1996)). (*see,* Office Action, page 10).

As detailed above, the combination of Sykes in view of Slavin, Nowak, and Mathias fails to render obvious Applicant's claimed invention. This deficiency is not cured by Bolotin.

Dependent claim 80 is drawn to the method of claim 29, further comprising administering a cytokine, a growth factor, or a combination of a cytokine and a growth factor to the patient. Dependent claim 81 is drawn to the method of claim 80, wherein the cytokine is selected from the group consisting of Interleukin 2 (IL-2), Interleukin 7 (IL-7), Interleukin 15 (IL-15), and combinations thereof.

The Office Action relies on Bolotin to teach the use of IL-7. However, Bolotin is directed to using IL-7 to promote thymic reconstitution and enhance thympoiesis after bone marrow transplantation (BMT) to prevent post-BMT immune deficiency. There is no teaching in Bolotin that remedies the deficiencies of the primary and secondary reference, either alone, or in combination.

Applicant notes that the instant claims as amended are not directed to improving engraftment after bone marrow transplantation (BMT), but rather to a method for treating or alleviating symptoms of an autoimmune disease in a patient having or suffering an autoimmune disease. One with ordinary skill in the art would not consider Bolotin to be applicable in treating or alleviating autoimmune disease in patients.

Because the combined references do not teach or suggest all claim limitations, Applicant respectfully submits that the grounds for this rejection have been overcome. Accordingly, Applicant respectfully requests that the Examiner reconsider and withdraw this rejection.

(c) Claims 80 and 82 stand rejected as purportedly being obvious over Sykes *et al.* (U.S. 5,658,564) in view of Slavin (U.S. 6,544,787), Nowak (New Scientist 19/26, page 11, January 2, 1999), and Mathias (U.S. 5,434,136), and further in view of Tian (*Stem Cells* **16**:193-99, 1998). (*see,* Office Action, page 11).

As detailed above, the combination of Sykes in view of Slavin, Nowak, and Mathias fails to render obvious Applicant's claimed invention. This deficiency is not remedied by Tian.

Dependent claim 80 is drawn to the method of claim 29, further comprising administering a cytokine, a growth factor, or a combination of a cytokine and a growth factor to the patient. Dependent claim 82 is drawn to the method of claim 80, wherein the growth factor is selected from the group consisting of a member of the epithelial growth factor family, a member of the fibroblast growth factor family, stem cell factor, granulocyte colony stimulating factor (G-CSF), keratinocyte growth factor (KGF), insulin-like growth factor, a growth hormone, a thyroid hormone, and combinations thereof.

The Office Action relies on Tian to teach that growth hormone promotes hematopoietic reconstitution after syngeneic BMT and to accelerate hematopoiesis after autologous BMT. Tian does not remedy the deficiencies of the primary and secondary reference, either alone or in combination.

Applicant notes that the instant claims as amended are not directed to improving engraftment after bone marrow transplantation (BMT), but rather to a method for treating or alleviating symptoms of an autoimmune disease in a patient having or suffering an autoimmune disease. One with ordinary skill in the art would not consider Tian to be applicable in treating or alleviating autoimmune disease in patients.

Because the combined references do not teach or suggest all claim limitations, Applicant respectfully submits that the grounds for this rejection have been overcome. Accordingly, Applicant respectfully requests that the Examiner reconsider and withdraw this rejection.

V. Provisional Obviousness-Type Double Patenting Rejections:

(a) Claims 29-33, 36-37, 39-42, 45, 47-50, 80-82, 92, 94-100, and 103 stand provisionally rejected under the judicially created doctrine of obviousness type double patenting as being unpatentable over claims 19-26, 28-40, 53, 55-66, 68, 71-72, and 74-75 of U.S. Appl. 10/749,119 (*see*, Office Action, page 14).

The currently amended claims of the instant application are generally directed to methods for treating or alleviating symptoms of an autoimmune disease in a patient having or suffering an autoimmune disease and methods for reducing the risk of developing an autoimmune disease in a patient at risk of having or suffering an autoimmune disease.

Claims 19-26, 28-40, 55-66, 69-72, and 74-75 of U.S. Appl. 10/749,119 are directed to methods for increasing tolerance in a patient to a graft from an MHC-mismatched donor. These claims do not in any way teach, suggest or motivate one of ordinary skill to arrive at the currently amended claims of the instant application.

Applicant respectfully submits that the preamble of the instant claims is to be given effect. "If . . . the claim preamble is 'necessary to give life, meaning, and vitality' to the claim, then the claim preamble should be construed as if in the balance of the claim." *Pitney Bowes, Inc. v. Hewlett-Packard Co.*, 182 F.3d 1298, 1305 (Fed. Cir. 1999). When that is properly done here, it is clear that one of ordinary skill in the art would have no reason to consider pursuing the steps of U.S. Appl. 10/749,119 to treat a patient with an autoimmune disease. The mere fact that the steps recited in the two applications may be similar, or that the patient pool may include similar patients, in no way renders the instant claims obvious. Similar steps may be practiced to accomplish completely non-obvious outcomes as in this case.

Accordingly, Applicant respectfully requests that this rejection under the judicially created doctrine of obviousness type double patenting be reconsidered and withdrawn.

CONCLUSION

Upon entry of the instant amendments to the claims, claims 29-30, 32-33, 36-42, 45, 47-50, 80-82, 92-100, and 103 will be pending in the instant application. Applicant respectfully submits that the claims are in condition for allowance and respectfully requests that a Notice of Allowance be issued.

Applicant petitions for a two-month extension of time to respond to the outstanding Office Action. Please charge the requisite payment to our Deposit Account No. 08-0219. Other than these fees no additional fees are believed to be due in connection with this correspondence; however, if any fees are due, or overpayments to be credited please charge the requisite payment or credit the overpayment to our Deposit Account No. 08-0219.

If a telephonic interview would advance prosecution of the application, the Examiner is invited to telephone the undersigned at the telephone number given below.

Respectfully submitted,

Dated: June 16, 2008

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